REMARKS

Claims 1-88 are pending in the application. Claims 43, 54, 67-69, and 77-88 are withdrawn from consideration and Claims 1-42, 44-53, 55-66, and 70-76 have been examined. Claims 1-42, 44-53, 55-66, and 70-76 stand rejected. Claims 1, 21, 22, 44, 57, 63, 65, and 70 have been amended. No new matter has been added. Applicants respectfully request reconsideration and allowance of Claims 1-42, 44-53, 55-66, and 70-76.

The Rejection of Claims Under 35 U.S.C. § 102(e)

The Examiner has rejected Claims 1-42, 44-53, 55-66, and 70-76 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,741,899 (Capon et al.). According to the Examiner, Capon et al. provides an enabling disclosure for making and using the vectors and cells for obtaining drug-induced proliferation of primary cells. Applicants respectfully disagree.

Claims 1-42, 44-53, 55-66, and 70-76 are directed to primary mammalian cells, including primary hematopoietic stem cells, and methods of making and using these cells, wherein the cells express fusion proteins comprising at least one drug binding domain and at least one signaling domain, which render the cells sensitive to drug-induced growth, proliferation, or differentiation. In the Amendment and Response to Paper No. 17, filed February 11, 2004, Claims 1, 21, 22, 44, 57, 63, 65, and 70, from which Claims 2-20, 23-43, 45-52, 58-62, 64-66, and 71-76 depend, were amended to recite that exposure of the cells to the drug reversibly induces growth, proliferation, or differentiation. According to the Examiner, the limitation "reversibly" is a property of the drug and does not distinguish the invention over Capon et al. Without acquiescing to the Examiner's position, Claims 1, 21, 22, 44, 57, 63, 65, and 70, from which Claims 2-20, 23-43, 45-52, 58-62, 64-66, and 71-76 depend, have been amended to delete the term "reversibly."

As stated in the M.P.E.P., "[t]he disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the

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subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Foundation for Medical and Education Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (At issue was whether a prior art reference enabled one of ordinary skill in the art to produce Elan's claimed transgenic mouse without undue experimentation. Without a disclosure enabling one skilled in the art to produce a transgenic mouse without undue experimentation, the reference would not be applicable as prior art.)." M.P.E.P. § 2121.01. For the following reasons and the reasons already of record in the Amendment and Response to Paper No. 17, filed February 11, 2004, applicants submit that Capon et al. does not provide an enabling disclosure of the claimed invention because undue experimentation would be required for one of skill in the art to obtain the claimed primary mammalian cells or to practice the claimed methods of making or using these cells.

Capon et al. describes placing CPR-expressing $CD8^+$ T cells in "culture dishes coated with saturating concentrations of either OKT4A, anti-human Fc Mab, gp120, gp160-expressing cells, gp41/gp120-expressing cells, HIV-1 infected cells or FK1012" (Col. 42, lines 61-64). The Inventor's Declaration submitted herewith (hereinafter "Second Blau Declaration") establishes that the method described in Capon et al. would not lead to drug-induced proliferation of primary mammalian cells, as described below (see Second Blau Declaration, paragraphs 5-7).

Saturating concentrations of a bivalent drug such as FK1012 inhibit growth by occupying all of the binding sites of its receptor and thereby preventing dimerization (see Second Blau Declaration, paragraph 6). For example, human growth hormone (hGH) is a bivalent molecule with two separate sites for binding to the extracellular domain of the human growth hormone receptor (hGHbp) (Fuh et al. (1992) *Science* 256:1677-80, page 1678, Col. 1; Fig. 1; enclosed). At low concentrations, hGH binds to both sites to produce an active complex containing a dimeric form of hGHbp $(hGHpb)_2$, thereby inducing proliferation (Fuh et al. (1992) *Science*

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256:1677-80, page 1678, Col. 1; Fig. 1). However, at high concentrations, human growth hormone saturates the receptor and acts as an antagonist by preventing dimerization (Fuh et al. (1992) *Science* 256:1677-80, page 1678, Col. 2; Fig. 1) (see also Second Blau Declaration, paragraph 6).

The same effect is observed with saturating concentrations of FK1012 (Second Blau Declaration, paragraph 7). Proliferation of Ba/F3 cells expressing a chimeric protein containing an intracellular signaling domain linked to a FKBP domain in response to FK1012 is concentration-dependent, and at higher concentrations of FK1012 less proliferation is observed (Blau et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94:3076-81, page 3078, Col. 1). The reason for the decline in cell proliferation with higher concentrations of FK1012 is suggested to be "due to excessive occupancy of the FKBP12 binding sites by FK1012, thus preventing oligomerization/dimerization of the fusion proteins" (Blau et al. (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94:3076-81, page 3078, Col. 1). Moreover, experimental results obtained in Dr. Blau's laboratory on June 2, 1997, show that saturating concentrations of FK1012 completely inhibit proliferation of cells expressing a similar chimeric protein (Second Blau Declaration, paragraph 7, Table 1, Figure 1).

Because Capon et al. teaches the use of saturating concentrations of FK1012, a person of skill in the art reading Capon et al. would not be able to practice the claimed methods without undue experimentation (Second Blau Declaration, paragraph 8). Therefore, the disclosure of Capon et al. does not enable a person of skill in the art to obtain the claimed primary mammalian cells (such as primary hematopoietic stem cells), or to practice methods of expanding these cells or methods of treating a hemopoietic disease or condition by exposing to a drug cells containing a construct coding for a fusion protein comprising at least one signaling domain and at least one drug-binding domain.

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For the reasons described above, applicants submit that Capon et al. does not anticipate the claimed invention. Nor does Capon et al. render obvious the claimed invention; in fact, Capon et al. teaches away from the claimed invention by specifying the use of saturating concentrations of a drug, which would inhibit cell proliferation. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Claims 1-42, 44-53, 55-66, and 70-76 are believed to be in condition for allowance. If any issues remain that can be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1783.

Respectfully submitted,

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